REMARKS

Previously, claims 1, 8-10, 12-13, 20, 28-30, and 33-36 were pending and under consideration. In the present paper, claims 1 and 28 are amended, claim 36 is cancelled, and new claims 40-43 are presented for consideration. Thus, following entry of the present amendment, claims 1, 8-10, 12-13, 20, 28-30, 33-35, and 40-43 remain pending and under consideration.

Applicants acknowledge the PTO's withdrawal of the rejections under 35 U.S.C. §§ 102(a) or 102(e), 102(b), and 103(a) and kindly thank the PTO for the same. The sole remaining rejection is addressed below.

I. The Amendments to the Claims

In the present paper, claims 1 and 28 are amended, claim 36 is cancelled, and new claims 40-43 are presented for consideration. As the amendments to the claims and the new claims are fully supported by the application as filed, no new matter is presented by the present amendment to the claims.

Specific support for the amendment to claims 1 and 28 may be found, for example, in the specification at page 26, lines 3-20, at page 27, lines 29-33, and in claims 1 and 28 as filed.

Support for new claim 40 may be found, for example, in the specification at page 24, lines 12-17, in Example 5, in Example 15, and in Example 17. Support for new claim 41 may be found, for example, in the specification at page 19, lines 11-18. Support for new claim 42 may be found, for example, in the specification at page 18, lines 18-23. Support for new claim 43 may be found, for example, in the specification at page 26, lines 3-12, at page 27, lines 29-33, and in claims 1 and 28 as filed.

As the amendments to the claims and the new claims are fully supported by the application as filed, they present no new matter. Accordingly, entry of the present amendment to the claims is hereby respectfully requested under 37 C.F.R. § 1.111.

II. The Rejection of Claims 1, 8-10, 12-13, 20, 28-30, and 33-36 as Obvious Should Be Withdrawn

Claims 1, 8-10, 12-13, 20, 28-30, and 33-36 stand rejected under 35 U.S.C § 103(a) as allegedly obvious over Rouy *et al.* (U.S. Patent No. 6,512,161) and Eggerman *et al.* (IDS 04-06-05) in view of GenBank Accession No. NM_000384, Monia *et al.* (U.S. Patent No. 5,656,612), Agrawal *et al.* (2000, *Mol. Med. Today*, 6(2): 72-81), and Wengel *et al.* (U.S. Patent Application Publication No. 2002/0068708A1).

In particular, the PTO contends that Rouy *et al.* teaches antisense oligonucleotides targeting apolipoprotein B mRNA comprising at least 20 nucleobases in length. The PTO acknowledges that Rouy *et al.* does not disclose the non-catalytic compounds comprising the various modifications recited in the instant claims. The PTO argues, however, that Monia *et al.* and Wengel *et al.* teach that one or more sugar modifications, phophorothioate modified internucleoside linkages, 5'-methylcytosine modified nucleobases, and LNA modifications are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds comprising these modifications. The PTO further acknowledges that neither Rouy *et al.* nor Eggerman *et al.* discloses non-catalytic compounds that are fully complementary to the nucleotide sequence set forth in SEQ ID NO:3. The PTO contends, however, that this deficiency is made up by the GenBank reference disclosing the nucleotide sequence encoding the full-length apolipoprotein B mRNA in combination with Agrawal *et al.*, which allegedly discloses designing antisense oligonucleotide to target the various regions of a known nucleotide sequence of a gene.

As initial matter, Applicants note that rejection of claim 36 is moot in view of its cancellation. Applicants further respectfully submit that none of the cited references, either alone or in combination, suggests to the artisan of ordinary skill that non-catalytic oligonucleotide compounds should be fully complementary to the nucleotide sequence set forth in SEQ ID NO: 3 excluding the start codon region as recited by each of the pending claims. Moreover, Agrawal *et al.*, as discussed below, specifically teaches away from excluding the start codon region, further demonstrating the non-obviousness of the claims.

A. The Legal Standard

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), the Supreme Court enunciated the standard for evaluating obviousness of a claimed invention. "[T]he scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." *Graham,* 383 U.S. at 17-18.

The Supreme Court recently articulated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007) the proper analysis for ascertaining the differences between the prior art and claimed invention under the *Graham* test. According to the Supreme Court, "it will be necessary for a court to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and the background

knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue," *Id.* at 1740-41. The Supreme Court further emphasized that "this analysis should be made explicit." *Id.* at 1741, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Moreover, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). In addition, one of ordinary skill in the art must have a reasonable expectation of success in achieving the claimed invention. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Where a *prima facie* case of obviousness has been met, it "can be rebutted if the applicant . . . can show 'that the art in any material respect taught away' from the claimed invention." *In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997), quoting *In re Malagari*, 499 F.2d 1297, 1303 (CCPA 1974). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference ... would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). It is improper to combine references where one of the references teach away from their combination. *See In re Grasselli*, 713 F.2d 731 (Fed. Cir. 1983).

B. The Cited References Do Not Teach or Suggest All Claim Limitations of the Claimed Invention

The combination of cited references fails to teach or suggest a non-catalytic oligonucleotide compound, 20 nucleobases in length, that is fully complementary to the nucleotide sequence set forth in SEQ ID NO: 3 excluding the start codon region. The primary reference cited by the PTO, Rouy *et al.*, neither teaches nor suggests that an antisense compound should be targeted to any particular region of apolipoprotein B. Rather, Rouy *et al.* discloses a transgenic rabbit that expresses a functional human apolipoprotein (a) and apolipoprotein B and only generally discloses a method for inhibiting their expression with antisense technology. As such, Rouy *et al.* certainly does not teach or suggest that the antisense oligonucleotide target region should exclude the start codon region.

Likewise, Eggerman *et al.* neither teaches nor suggests that an antisense compound should be targeted to any particular region of apolipoprotein B. While Eggerman *et al.* states that apolipoprotein B mRNA production may be inhibited up to 80% in a human liver cell

line, the reference fails to disclose a single oligonucleotide or concentration at which the oligonucleotide is effective. Thus, nothing in Eggerman *et al.* suggests to the artisan of ordinary skill that the antisense oligonucleotide target region should exclude the start codon region, and as such, inclusion of Eggerman *et al.* in the combination of references cited does not cure the deficiencies of the combination.

Furthermore, none of the secondary references cited by the PTO, either alone or in combination, teach or suggest that antisense oligonucleotide target region should exclude the start codon region. For example, while Agrawal *et al.* addresses, *inter alia*, antisense target site selection, it does not teach that the start codon region should be excluded. Agrawal *et al.* merely suggests that oligonucleotides that encompass different regions on the mRNA should be screened. Agrawal *et al.* at p. 77, col. 1, paragraph 1. In contrast to the presently claimed subject matter, Agrawal *et al.* explicitly teaches that translation initiation codon region *should* be targeted because oligonucleotides that are targeted to the start codon region are more potent than those targeted to other regions, though it may be difficult to identify suitable oligonucleotides targeted to this region in some circumstances. *Id.* Addition of Agrawal *et al.* to the combination of cited references, therefore, does not remedy the deficiency of the combination. In fact, as discussed below, Agrawal *et al.* actually teaches away from the presently claimed invention.

Finally, the inclusion of Monia *et al.*, Wengel *et al.*, and GenBank Accession No. NM_000384 also fails to produce a combination of references that teach or suggest each of the claims of the present invention. Monia *et al.* teaches that oligonucleotide modifications, such as phosphorothioates, are known to both increase hybridization efficiency and nuclease resistance of oligonucleotide compounds, as applied to raf gene expression modulation. Monia *et al.* does not disclose, however, that the start codon region should be excluded when targeting the modified oligonucleotides to raf gene or any other genes. Wengel *et al.* teaches that LNA modifications increase the hybridization affinity. Wengel *et al.* also does not disclose anything regarding antisense target selection and certainly does not disclose that the start codon region should be excluded. GenBank Accession No. NM_000384 discloses only the nucleic acid sequence encoding human apolipoprotein B protein. It does not teach anything regarding antisense target selection, and specifically, does not teach or suggest that antisense oligonucleotide target selection should exclude the start codon region.

Thus, the combination of the references cited fails to provide a reason why one of ordinary skill in the art should select an antisense oligonucleotide target region excluding the start codon region of apolipoprotein B mRNA. Absent such a reason, the PTO cannot

establish obviousness of the present claims under the controlling standard articulated by the Supreme Court. *See KSR* at 1740-41. Applicants therefore respectfully request that the obviousness rejection under 35 U.S.C. § 103(a) be withdrawn.

C. Agrawal *et al.* Teaches Away from the Claimed Invention

In addition to the arguments presented above, Applicants respectfully submit that Agrawal *et al.* specifically teaches away from the claimed invention. In particular, Agrawal *et al.* teaches away from a non-catalytic oligonucleotide compound that is fully complementary to the nucleotide sequence set forth in SEQ ID NO: 3 excluding the start codon region.

At the paragraph bridging pages 76 and 77 of Agrawal *et al.*, the authors discuss the initial step in choosing an appropriate target sequence on the mRNA molecule. The authors state that "it is considered preferable to screen a number of oligonucleotides that encompass different regions on RNA" including the initiation codon site. Agrawal *et al.* at p. 77, col. 1, paragraph 1. Importantly, though, the authors teach that "[o]ligonucleotides that have been targeted to the translation initiation codon region of mRNA are generally believed to be more potent than those targeted to other regions." *Id.* Thus, upon reading Agrawal *et al.* as a whole, in combination with the other cited references, a person of ordinary skill would be motivated to target antisense oligonucleotides to the start codon region of apolipoprotein B. Applicants, in contrast, specifically exclude the start codon region in the presently pending claims. Because Agrawal *et al.* leads a person of ordinary skill in a direction divergent from the path that is taken by Applicants, the reference teaches away from the claimed invention. *See Tec Air, Inc.*, 192 F.3d at 1360.

While Agrawal *et al.* favors targeting the translation start region, it indicates that it can be difficult to find an antisense target site that both includes the initiation codon and satisfies all the criteria discussed in the reference for optimal antisense oligonucleotide design. See Agrawal *et al.*, p. 77, col. 1, paragraph 1. According to Agrawal *et al.* such criteria include avoiding G-rich (GGGG) motifs, which can induce cell proliferation and immune response, and avoiding self-complementarity or palindromic sequences, which can form stable secondary structures, such as short linear duplexes or hairpins. *See* Agrawal *et al.* p. 77, col. 2, paragraph 1-2. In addition, the authors indicate that CpG motifs should be avoided, citing three references (Kuramoto *et al.*, *Jpn. J. Cancer Res.*, 83(11): 1128-1131 (1992); Krieg *et al.*, *Nature*, 374: 546-549 (1995); and Zhao *et al.*, *Biochem. Pharmacol.*, 51(2): 173-82(1996)). *See* Agrawal *et al.* at p77, col. 2, paragraph 1.

In Kuramoto *et al.* and Zhao *et al.*, the authors show that oligonucleotides containing CpG motifs within palindromic sequences induce natural killer cell activation and cell proliferation. In Krieg *et al.*, the authors show that CpG motifs flanked by two 5' purines (preferably a GpA dinucleotide) and two 3' pyrimidines (preferably a TpC or TpT dinucleotide) induce B-cell activation, indicating that the sequence context of the CpG dinucleotide is important in immune response. Krieg *et al.* at p. 546, col. 2, paragraph 3. Thus, the ordinarily skilled artisan would recognize from these references that CpG motifs within palindromic sequences or flanked by two 5' purines and two 3' pyrimidines should be avoided.

One of ordinary skill in the art applying these criteria to apolipoprotein B would conclude that, in fact, the start codon region of apolipoprotein B could and, therefore should, be targeted. For example, in the sequences of SEQ ID NO: 3, there are 18 possible 20-nucleobase oligonucleotides that contain the complementary sequence to the start codon, ATG. For the PTO's convenience these oligonucleotides and their properties are provided in a table shown as Exhibit A. As shown in Exhibit A, 11 out of the 18 possible oligonucleotide sequences lack self complementarity or palindromic sequences (determined by OligoCalc available at http://www.basic.northwestern.edu/biotools/oligocalc.html) and lack GGGG motifs. Furthermore, none of the 11 oligonucleotide sequences contain CpG motifs within palindromic sequences or CpG motifs that are flanked by two 5' purines and two 3' pyrimidines. Certainly, none of the 11 oligonucleotide sequences contain CpG motifs flanked by 5' GpA or 3' TpC or TpT dinucleotides, which robustly induce B-cell activation. Therefore, according to the teachings of Agrawal *et al.* and its cited references, oligonucleotides complementary to the start codon region of apolipoprotein B that satisfy the criteria of Agrawal *et al.* readily can be identified by one of ordinary skill in the art. Accordingly Agrawal *et al.* teaches that the start codon region should be targeted by antisense oligonucleotide compounds.

In contrast to these teachings, however, Applicants specifically claim antisense oligonucleotide compounds that target the nucleotide sequence set forth in SEQ ID NO: 3 *excluding* the start codon region. Since Agrawal *et al.* teaches away from antisense compounds targeted to the nucleotide sequence excluding the start codon region of apolipoprotein B, Agrawal *et al.* cannot be used as part of an obviousness rejection. Further, the teaching away by Agrawal *et al.* provides affirmative evidence of non-obviousness. Accordingly, for at least this additional reason, the presently pending claims are not obvious over the combination of references cited by the PTO.

D. The Cited References Do Not Teach or Suggest All Claim Limitations of Claim 13

In addition to the arguments presented above, Applicants respectfully submit that the cited references fail to teach or suggest the composition recited by claim 13. In particular, none of the cited references, either alone or in combination, teach or suggest a colloidal dispersion system. While Rouy *et al.*, Monia *et al.*, and Wengel *et al.* might generally discuss pharmaceutical compositions capable of delivering antisense nucleic acid constructs, none of these references teach or suggest a composition comprising a colloidal dispersion system, as recited by claim 13.

Moreover, Agrawal *et al.* does not teach or suggest anything regarding compositions or pharmaceutical carriers. It certainly does not disclose a composition comprising a colloidal dispersion system, as presented in claim 13. Likewise, GenBank Accession No. NM_000384 only sets forth the nucleic acid sequence encoding human apolipoprotein B protein and does not disclose anything regarding pharmaceutical carriers or compositions comprising a colloidal dispersion system.

Thus, all the claim limitations of claim 13 are not taught or suggested by the cited combination of references. Accordingly, for at least this additional reason, claim 13 is not obvious over the combination of references cited by the PTO.

E. The Cited References Do Not Teach or Suggest All Claim Limitations of Claim 29 and Claim 30

In addition, Applicants note that the cited references additionally fail to teach or suggest the specific regions of SEQ ID NO: 4 recited by claim 29 and claim 30. In particular, none of the cited references, either alone or in combination, teach or suggest the target sequence ranges of claim 29, which targets nucleotides 1 to 103 or 157 to 14121 of SEQ ID NO: 3, or claim 30, which targets nucleotides 1 to 79 or 182 to 14121 of SEQ ID NO: 3. As extensively discussed above, the combination of references neither teaches or suggests that an antisense compound should be targeted to any particular region of apolipoprotein B, other than the translation start codon region. They certainly do not teach or suggest that one of ordinary skill in the art should target nucleotides 1 to 103 or 157 to 14121, as presented in claim 29, or nucleotides 1 to 79 or 182 to 14121, as presented in claim 30. Thus, each of the claim limitations of claim 29 and claim 30 is not taught or suggested by the cited references. Accordingly, for at least this additional reason, claim 29 and claim 30 are not obvious over the combination of references cited by the PTO.

F. The Obviousness Rejection Should Be Withdrawn

Applicants respectfully submit that the references cited by the PTO, whether considered alone or in combination, fail to teach or suggest each and every element of the invention recited by the independent claim 1 of the present application. Thus, Applicants respectfully submit that neither claim 1 nor any of its dependent claims is not obvious over the combination of references cited by the PTO. Further, Applicants respectfully submit that claim 13, claim 29, and claim 30 are not obvious over the references cited by the PTO as the references, alone or in combination, fail to teach or suggest the additional limitations of these claims. Therefore, Applicants respectfully request that the rejection of claims 1, 8-10, 12-13, 20, 28-30, and 33-36 under 35 U.S.C. § 103(a) as obvious over Rouy *et al.* and Eggerman *et al.* in view of GenBank Accession No. NM_000384, Monia *et al.*, Agrawal *et al.*, and Wengel *et al.* be withdrawn.

CONCLUSION

In light of the above remarks, Applicants respectfully request that the PTO reconsider this application with a view towards allowance. The Examiner is invited to call the undersigned attorney at (650) 739-3949, if a telephone call could help resolve any issues.

Respectfully submitted,

Date: October 30, 2007

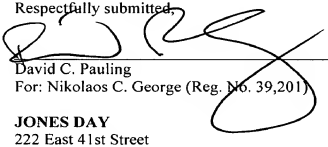

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EXHIBIT A

Apolipoprotein B Oligonucleotide Sequences and Motifs Per Agrawal et al.

There are 18 possible 20-mer oligonucleotides that contain the start codon (atg) in SEQ ID NO. 3: 5'-cccca ccgca gctgg cgatg gaccc gccga ggccc gc-3'

11 out of 18 antisense oligonucleotide sequences do not contain a GGGG motif, self-complementarity, or hairpin motifs. Self-complementarity and hairpin motifs were determined by http://www.basic.northwestern.edu/biotools/oligocalc.html

apoB nucleotide sequence 5'-3' (20bp) SEQ ID NO. 3	Complementary antisense sequence 5'-3' (20bp)	CpG motifs	GGGG motifs	Self-complementary motifs	Hairpin motifs
ccccaccgcagctggcgatg	catcgccagctgcggtgggg	2	1	None	None
cccaccgcagctggcgatgg	ccatcgccagctgcggtggg	2	None	2	None
ccaccgcagctggcgatgga	tccatcgccagctgcggtgg	2	None	2	None
caccgcagctggcgatggac	gtccatcgccagctgcggtg	2	None	None	None
accgcagctggcgatggacc	ggtccatcgccagctgcggt	2	None	None	None
ccgcagctggcgatggaccc	gggtccatcgccagctgcgg	2	None	None	None
cgcagctggcgatggacccg	cgggtccatcgccagctgcg	3	None	None	None
gcagctggcgatggacccgc	gcgggtccatcgccagctgc	2	None	None	None
cagctggcgatggacccgcc	ggcgggtccatcgccagctg	2	None	None	1
agctggcgatggacccgccg	cggcgggtccatcgccagct	3	None	None	1
gctggcgatggacccgccga	tcggcgggtccatcgccagc	3	None	None	1
ctggcgatggacccgccgag	ctcggcgggtccatcgccag	3	None	None	1
tggcgatggacccgccgagg	cctcggcgggtccatcgcca	3	None	None	None
ggcgatggacccgccgaggc	gcctcggcgggtccatcgcc	3	None	None	None
gcgatggacccgccgaggcc	ggcctcggcgggtccatcgc	3	None	None	None
cgatggacccgccgaggccc	gggcctcggcgggtccatcg	3	None	None	None
gatggacccgccgaggcccg	cgggcctcggcgggtccatc	3	None	None	None
atggacccgccgaggcccgc	gcgggcctcggcgggtccat	3	None	None	None